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From Conventional Radiotracer Tc-99^{m} with Blue Dye to Indocyanine Green Fluorescence: A Comparison of Methods Towards Optimization of Sentinel Lymph Node Mapping in Early Stage Cervical Cancer for a Laparoscopic Approach

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ABSTRACT

Background. The credibility of sentinel lymph node (SLN) mapping is becoming increasingly more established in cervical cancer. We aimed to assess the sensitivity of SLN biopsy in terms of detection rate and bilateral mapping in women with cervical cancer by comparing technetium-99 radiocolloid (Tc-99^{m}) and blue dye (BD) versus fluorescence mapping with indocyanine green (ICG).

Methods. Data of patients with cervical cancer stage 1A2 to 1B1 from 5 European institutions were retrospectively reviewed. All centers used a laparoscopic approach with the same intracervical dye injection. Detection rate and bilateral mapping of ICG were compared, respectively, with results obtained by standard Tc-99^{m} with BD.

Results. Overall, 76 (53 %) of 144 of women underwent preoperative SLN mapping with radiotracer and intraoperative BD, whereas 68 of (47 %) 144 patients underwent mapping using intraoperative ICG. The detection rate of SLN mapping was 96 % and 100 % for Tc-99^{m} with BD and ICG, respectively. Bilateral mapping was achieved in 98.5 % for ICG and 76.3 % for Tc-99^{m} with BD; this difference was statistically significant ($p < 0.0001$).

Conclusions. The fluorescence SLN mapping with ICG achieved a significantly higher detection rate and bilateral mapping compared to standard radiocolloid and BD technique in women with early stage cervical cancer. Nodal staging with an intracervical injection of ICG is accurate, safe, and reproducible in patients with cervical cancer. Before replacing lymphadenectomy completely, the additional value of fluorescence SLN mapping on both perioperative morbidity and survival should be explored and confirmed by ongoing controlled trials.

Sentinel lymph node (SLN) biopsy has changed the management of patients with breast cancer and melanoma and has been integrated into the standard treatment of selected patients with early stage vulvar cancer.[1]

Nodal status still represents the most important prognostic factor of surgically staged patients with early stage cervical cancer. Despite substantial positive evidence supporting the integration of SLN biopsy into the routine clinical management of women with an early stage disease, the accuracy of this procedure still needs to be addressed in a prospective fashion.

The standard accepted method that has achieved the best results for SLN biopsy includes the combination of radiocolloid and blue dye (BD). Literature reports a detection

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rate ranging from 70 to 93 %.[2,3] However, recently, great efforts have been made worldwide to find a more efficient and reliable tracer.

Indocyanine green (ICG) is a fluorescent dye that has been used in a variety of applications in medicine since the 1950s, but only recently have its fluorescent properties been evaluated for SLN mapping of a variety of solid tumors.[4–6] Near-infrared fluorescent imaging with ICG has been widely investigated and has emerged as a promising alternative technique for real-time intraoperative SLN mapping in gynecologic cancer. The higher sensitivity and bilateral mapping compared to the combined technique or BD alone, together with the steep learning curve of traditional laparoscopy, allows surgeons to easily identify the lymphatic channels and the SLNs, even in an anatomic region that is unlikely to be explored during routine lymphadenectomy.[7] Surgical and anesthesia time can be reduced, which consequently may reduce the costs and risks associated with surgery. This technique, together with a minimally invasive laparoscopic approach, appears to be widely applicable and represents a valid tool compared to robotic surgery, particularly in those countries and centers where a robot platform is not available.

The primary objective of this multicenter European study was to compare the traditional combined technique using technetium-99 radiocolloid (Tc-99^m) and BD and ICG fluorescent dye in terms of detection rate and bilateral mapping in patients with early stage cervical cancer undergoing radical surgery with a traditional laparoscopic approach.

MATERIALS AND METHODS

Patients

Between 2008 and 2015, women with stage 1A2 to 1B1 cervical cancer were enrolled onto this study from five European centers (Monza, Berne, Madrid, Varese, and Rome). All women underwent planned minimally invasive, radical laparoscopic radical surgery, including SLN mapping with bilateral pelvic lymphadenectomy.

The SPIES Full HD Image 1S H3-Z FI camera with the Karl Storz Near Infrared (NIR/ICG) System (Karl Storz Endoscopy, Mittelstrasse, Tuttlingen, Germany) was used by all the participating centers. All patients provided written informed consent, and the local institutional review boards approved the study.

Preoperative Lymphoscintigraphy

In 3 centers (Monza, Berne, and Madrid) SLN mapping was performed using the combined radioisotopic technique and the BD intraoperative injection until the introduction of the fluorescence mapping with ICG.

Preoperative LSG was performed using 200 to 300 μCi of radiolabeled filtered Tc-99^m albumin nanocolloid, injected into the quadrants of the cervix on the day before surgery. After the injection, a dynamic 10-min planar anterior LSG (10 frames at 1 min per frame) was carried out, followed by planar anterior static images, performed immediately after the dynamic acquisition. When required, a single-photon emission computed tomography/computed tomography (SPECT/CT) study was performed 3 h after the radiotracer injection, with a hybrid system composed of a dual-head gamma camera with a low-dose X-ray tube installed in its gantry (Infinia Hawkeye 4, GE Medical Systems). The overall acquisition time of a SPECT/CT study was approximately 20 min. Images were analyzed on a Xeleris workstation (GE Medical Systems).

Intraoperative Tracer Injection

A total of 4 mL of BD (methylene blue 1 %) was injected. Two milliliters per injection for each side was administered at the 3 and 9 o'clock positions. The 12 o'clock injection was eliminated in order to avoid staining the vesicocervicovaginal space of the tumor. The injection of the BD or ICG was the same for all the involved centers. The ICG (Pulsion Medical Systems, Feldkirchen, Germany) concentration used was 1.25 mg/mL. For each patient, a 25 mg vial with ICG powder was diluted in 20 mL of aqueous sterile water. Four to 5 mL of this ICG solution was injected into the cervix alone, divided into the 3 and 9 o'clock positions. One milliliter of ICG solution was injected with penetration to a depth of 1 cm into the stroma, and 1 mL was injected into the submucous layer on the right and the left of the cervix, usually after the induction of general anesthesia. In one center (Berne), patients were injected with 8 to 10 mL of ICG using the same technique.

Pathology Evaluation

The disease of all women was staged after definitive histology according to the 2009 classification of the International Federation of Gynecology and Obstetrics. An expert gynecologic oncology pathologist, highly skilled in the analysis of SLNs, evaluated all surgical samples and SLNs. All lymph nodes were handled in a standardized manner.[8] SLNs with macroscopic metastases were sectioned, and the SLNs that appeared normal were cut perpendicular to the long axis. Two adjacent 5 μm sections were cut at each of 2 levels 50 μm apart from each block lacking metastatic carcinoma detectable in a routine section stained with

hematoxylin and eosin (H&E). At each level, one slide was stained with H&E and the other with immunohistochemistry using the AE1/AE3 anticytokeratin antibody (Dako, Glostrup, Denmark). One negative control slide in the total of five slides per block were stained as well. All other non-SLNs were only examined by routine H&E.

Micrometastasis was defined as a metastatic deposit within the SLNs ranging from 0.2 mm to no more than 2 mm in size. Isolated tumor cells (ITC) were defined as single tumor cells or cluster of malignant epithelial cells less than 0.2 mm.

Statistical Analysis

Absolute and percentage frequencies were used to describe categorical items, while median values and ranges were assessed for continuous variables. Rank sum test and Fisher's exact test were used to analyze the differences between the two groups. Stata 9.0 (StataCorp, College Station, TX, USA) was used for performing the statistical analysis. The alpha error was set at 5 % for all comparisons.

RESULTS

Overall, 144 women with early stage 1A2 to 1B1 cervical cancer from the five European centers underwent SLN mapping. Seventy-six patients (53 %) underwent mapping with the standard combination of Tc-99^{m}-positive BD, whereas the SLN mapping was performed with ICG in 68 patients (47 %) (Fig. 1). As shown in Table 1, the distribution of pretreatment characteristics such as age, body mass index, International Federation of Gynecology and Obstetrics stage, presence of lymphovascular space invasion, and the count of SLNs removed were balanced between the groups. There was a higher proportion of G1 tumors in the Tc-99^{m} group. The median number of SLNs was 2 (range 0–7) in the Tc-99^{m} group and 3 (range 1–15) in ICG group.

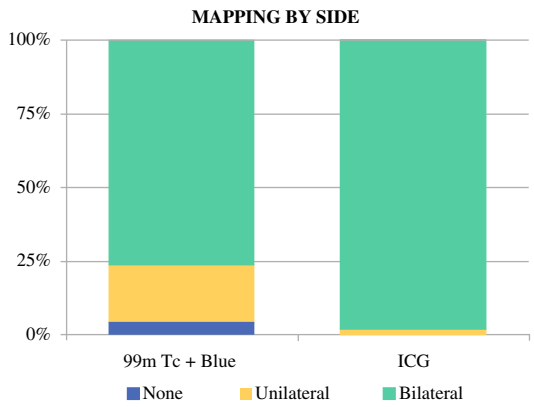

FIG. 1 Plot of SLN mapping by side between groups

The surgical characteristics of the study groups are displayed in Table 2. The overall detection rate of SLN mapping was 96 % and 100 % in the Tc-99^{m} and ICG groups, respectively. Tumor diameter was <2 cm in 56 % (43/76) and 51 % (35/68) in the Tc-99^{m} and ICG groups, respectively. A higher bilateral detection rate was achieved in the ICG group (98.5 vs. 76.3 %), and this difference was statistically significant ($p < 0.0001$).

While in patients with a tumor diameter less than 2 cm there was no significant difference between the two groups in terms of bilateral mapping ($p = 0.156$), in the case of a tumor bigger than 2 cm, bilateral mapping was significantly higher in the ICG group (100 vs. 64 %; $p = 0.001$).

SLN metastases were discovered in 17 (22 %) of 76 women in the Tc-99^{m} group and in 10 women (14.9 %) in the ICG group. Among the 3811 SLNs removed in 144 patients, only 60 presented metastasis (1.6 %). Overall, 41 (9.3 %) of 438 SLNs were positive, including 27 macrometastases (66 %), 12 positive SLNs had micrometastasis (29 %), and two nodes presented only ITC deposits (5 %). Finally, SLN was the only positive node in 7 of 10 patients in the ICG group and in 15 of 17 in the radiocolloid group. Table 3 shows the number and the type of metastases in per-patient and per-SLN analyses. There was only one false-negative SLN; therefore, the sensitivity, negative predictive value, and the false-negative rate were 96, 99, and 0.04 %, respectively.

DISCUSSION

In 2015, the members of the National Comprehensive Cancer Network recommended the SLN technique (evidence level 2B) for both early stage cervical and endometrial cancer.[9,10] Furthermore, the panel stressed that adherence to the algorithm is key to the success of the technique and that better detection can be achieved in tumors <2 in diameter.[11,12]

In that same period, the systematic review of Kadkhodayan et al. confirmed that SLN represents an accurate method for lymph node staging and for identifying small-volume disease in the SLN (i.e., micrometastasis and ITC) in patients with cervical cancer.[13] Moreover, the lowest false-negative rate was achieved in the subgroup of women with tumors <2 cm in diameter and at a lower stage.

In the significant amount of recent literature that focuses on SLN in cervical tumors, the only multicenter prospective trial that evaluated the ultrastaging of SLNs was the SENTICOL (French Ganglion Sentinelle dans le Cancer du Col) study.[14] In this study, 139 women with stage IA1 to IB1 disease underwent SLN mapping with the standard technique: an intracervical injection including radiocolloid

TABLE 1 Characteristics of 144 patients

Characteristic	Tc-99^{m} + blue dye (n = 76)	ICG (n = 68)	p
Age, years, median (range)	47 (26–85)	42 (25–75)	0.263[a]
BMI, kg/m^2, median (range)	24.0 (18–41)	23.7 (16–35)	0.852[a]
Tumor diameter			0.474[b]
>2 cm	35 (46.1 %)	30 (44.1 %)	
<2 cm	41 (53.9 %)	38 (55.9 %)	
pT stage (final pathology)			0.681[b]
CIS-IA	8 (10.5 %)	10 (14.7 %)	
IB1-IIA1[c]	68 (89.5 %)	58 (85.3 %)	
Histology (final pathology)			0.559[b]
Squamous	55 (72.4 %)	49 (72.1 %)	
Adenocarcinoma	20 (26.3 %)	16 (23.5 %)	
Clear cells	1 (1.3 %)	3 (4.4 %)	
Grade			0.001[b]
CIS	1	4	
G1	13 (17.3 %)	0	
G2	34 (45.3 %)	35 (59.3 %)	
G3	28 (37.3 %)	24 (40.7 %)	
NA	0	5	
LVSI			0.392[b]
Yes	30 (42.3 %)	25 (38.5 %)	
No	41 (57.7 %)	40 (61.5 %)	
NA	5	3	

BMI body mass index, *Tc-99^{m}* technetium-99 radiocolloid, *ICG* indocyanine green, *NA* not available, *LVSI* lymphovascular space invasion

[a] Rank sum test

[b] Fisher's exact test

[c] Including 6 cases of IIA1 stage at final pathology with cervical tumor diameter <4 cm

Tc-99^{m} and BD, followed by pelvic lymphadenectomy. The sensitivity of the whole population was 92 %, but it reached 100 % in the subgroup of patients with bilateral SLN mapping (77 %). Those results were confirmed in the study by Cibula et al., a retrospective multicenter study that recorded a 91 % sensitivity in SLN ultrastaging, which improved to 97 % in the case of bilateral SLN mapping, which resulted in a false-negative rate of 1.3 %.[15] One of the most important aspects of SLN mapping is the detection of at least one SLN for each hemipelvis. The adherence to SLN mapping algorithms is important and allows achieving a low and acceptable false-negative rate.[10] Thus, in the case of failed mapping in a hemipelvis, a side-specific lymphadenectomy should be performed, and all or any suspicious peritoneal findings or enlarged lymph nodes must be evaluated or sampled regardless of the SLN mapping. Moreover, the recent study by Cibula et al. highlights the possible impact on survival of low-volume disease discovered in the SLNs.[16] Despite the fact that the impact of low-volume disease on overall and progression-free survival is not completely clear, the overall survival of patients with micrometastasis (7.1 %) was similar to patients with macrometastasis, and it was statistically significant compared to patients with negative SLNs ($p <$ 0.001).

The possibility of avoiding the use of a radioactive agent such as technetium—which exposes patients to ionizing radiation and creates many logistical challenges for both hospital and patients—has prompted the study of new technologies and dyes such as ICG.

The real-time fluorescence of ICG eliminates the necessity of a exposing a patient to radioactivity and does not delay the planned surgical schedule. Therefore, it signifies that this procedure can also be performed in countries without access to nuclear medicine.

Fluorescent SLN mapping using ICG was first reported by Furukawa et al. in 2010 in patients with cervical cancer.[17] However, Rossi and colleagues had published the first report on ICG in a minimally invasive platform, reporting the feasibility of robot-assisted SLN mapping in 20 cases of cervical and endometrial cancer.[18] The detection rate was 85 % (17/20 patients), with a bilateral

TABLE 2 SLN mapping and lymph node characteristics according to dye used (n = 144)

Characteristic	Tc-99^{m} + blue dye (n = 76)	ICG (n = 68)	p
Lymph node surgical staging, median (range)	22 (3–82)	22 (2–67)	0.855[a]
SLN per patient, median (range)	2 (0–7)	3 (1–15)	0.047[a]
Mapping by side			<0.0001[b]
None	3 (3.9 %)	0	
Unilateral	15 (19.7 %)	1 (1.5 %)	
Bilateral	58 (76.3 %)	67 (98.5 %)	
Bilateral mapping			0.156
Tumor <2 cm	37 (88 %)	34 (97 %)	0.001
Tumor >2 cm	21 (64 %)	33 (100 %)	
Patients with positive SLN	17 (22.0 %)	10 (14.9 %)	0.168[b]
Positive SLN	24/203 (11.8 %)	17/241 (7.1 %)	0.059[b]

SLN sentinel lymph node, *Tc-99^{m}* technetium-99 radiocolloid, *ITC* isolated tumor cell

[a] Rank sum test

[b] Fisher's exact test

detection of 60 %. Since this preliminary report, a large quantity of literature has demonstrated a favorable, reliable, and time-efficient method of fluorescent real-time imaging with ICG for SLN mapping, and interest in its clinical application is growing. The largest published study of laparoscopic robot-assisted surgery, that of Jewell et al., evaluated the sensitivity of ICG in 227 women whose disease was surgically staged by applying the SLN algorithm for uterine or cervical cancer.[19] Thirty control cases received a combined intracervical injection of both ICG and BD. The overall detection rate of the SLN for the whole group of patients was 95 % (216/227), and the addition of BD did not improve the bilateral detection of SLN (ICG 79 vs. BD 77 %). In our study, we observed a higher detection rate (100 %) and also a higher rate of bilateral mapping (98.5 %) compared to the latter studies. However, our study population is less heterogeneous because it includes only early stage cervical cancer patients, which represents the most favorable group to undergo SLN mapping.[12]

Recent reports have also confirmed these excellent results for both traditional laparoscopy and robotic approaches.[20–22] Our large, retrospective, multicenter European study assessed the impact of fluorescent SLN mapping with ICG in patients with early stage cervical cancer compared to traditional mapping with radiocolloid and BD. In our study, real-time fluorescence using ICG demonstrated a higher detection rate and bilateral mapping compared to Tc-99^{m} and BD, and the differences are statistically significant ($p < 0.0001$). While in patients with tumor <2 cm in diameter there was no significant difference between the 2 groups in terms of bilateral mapping (p = 0.156), in the case of a tumor >2 cm in size bilateral mapping was significantly higher in the ICG group (100 vs. 64 %; p = 0.001). Thus, the dimension of a primary cervical lesion seems to affect the nodal mapping performed by ICG with respect to the traditional method less.

The false-negative rate of our study was 0.04 % because we recorded only one false-negative case. The woman was recruited in a center that had just started the experience with SLN mapping. The learning curve of SLN is well established, and around 30 cases per surgeon are required before achieving a good detection rate.[23] However, the evolution of the techniques of mapping, the dedicated efforts of the surgical team involved, and the introduction of new agents for mapping, such as fluorescent dye, will probably shorten the learning curve for the surgeons approaching to SLN mapping for the first time.

Recent experience underlines the importance of low-volume nodal metastases detected only by enhanced pathologic ultrastaging in order to avoid incorrectly defining a significant number of patients as having node-negative disease.[16,24] Furthermore, later studies have analyzed the impact on survival of micrometastasis and ITC in patients with uterine tumors who underwent SLN mapping.[25,26] Patients with low-volume metastasis received adjuvant therapy and had improved oncologic outcomes compared to those with lymph node macrometastasis. These results are further important reasons for continuing the evaluation of nodal staging with this promising technique. Starting from historical anatomic studies, cervical cancer represents the best anatomic location for intracervical SLN mapping. The in vivo experience faithfully replicates the studies on cadavers regarding the lymphatic drainage of the cervix.[27] Indeed, the fluorescent dye technique increases the sensitivity and reliability of this staging

TABLE 3 Per-SLN and per-patient analysis of type of metastasis by dye group (n = 27)

Analysis	Type of metastasis	Tc-99^{m} + blue dye	ICG
Per SLN	No. of positive SLNs	24	17
	Macrometastasis	13 (54.2 %)	14 (82.4 %)
	Micrometastasis	10 (41.7 %)	2 (11.7 %)
	ITC	1 (4.1 %)	1 (5.9 %)
Per patient	No. of patients with positive SLN	17	10
	Macrometastasis	8 (47.1 %)	7 (70 %)
	Micrometastasis	6 (35.3 %)	2 (20 %)
	Macro + micrometastasis	2 (11.8 %)	0 (0 %)
	ITC	1 (5.8 %)	1 (10 %)

SLN sentinel lymph node, *Tc-99^{m}* technetium-99 radiocolloid, *ITC* isolated tumor cell, *ICG* indocyanine green

approach, with a bilateral mapping rate of 98.5 % achieved in the whole study group.

Real-time florescence with ICG represents a new tool for SLN mapping, particularly in patients with cervical cancer, and it seems to have several advantages over BD and radiocolloid tracers. The SPIES system for traditional laparoscopy allows surgeons to have an excellent high-definition view of the lymphatic channels and of the SLN in the operative field, with the aid of a second-generation fluorescence device.[20–22,28] The fluorescent technology is available for both standard and robotic laparoscopy as well as for open surgery.[29] In addition, the use of the minilaparoscopic approach can further reduce overall surgical trauma in selected patients with early stage disease.[30] The lymphatic channels become visible under bright fluorescent light, which allows the surgeon to follow the lymphatic channels even in the case of atypical drainage pathways. The main drawback of our study is its retrospective design. However, our ICG intracervical injection protocol was standardized between the centers, as was the lymphoscintigraphy protocol in terms of radiocolloid injection and imaging acquisition.

The use of the ICG eliminates the necessity of radiotracer injection and preoperative lymphoscintigraphy in nuclear medicine, avoiding exposure to radiation for both patients and healthcare workers. In addition, it can have less of an unfavorable impact on patients' quality of life by facilitating the work flow and operative time of the surgical operations.

In conclusion, near real-time infrared fluorescent imaging represents an innovative and highly reproducible technique for SLN mapping in early stage cervical cancer. ICG mapping resulted in a significantly higher detection rate and bilateral mapping compared to the standard combined radiocolloid and BD technique. This new technique can lead to the reduction of side-specific lymphadenectomy, required in cases where only unilateral SLN mapping is achieved, with a consequent reduction in the duration and additional costs of surgical treatment. Results of ongoing randomize trials are anxiously awaited to confirm and assess the validity of these promising results.

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REFERENCES

1. Covens A, Vella ET, Kennedy EB, Reade CJ, Jimenez W, Le T. Sentinel lymph node biopsy in vulvar cancer: systematic review, meta-analysis and guideline recommendations. *Gynecol Oncol.* 2015;137:351–61.
2. van de Lande J, Torrenga B, Raijmakers PG, et al. Sentinel lymph node detection in early stage uterine cervix carcinoma: a systematic review. *Gynecol Oncol.* 2007;106:604–13.
3. Bats AS, Frati A, Mathevet P, et al. Contribution of lymphoscintigraphy to intraoperative sentinel lymph node detection in early cervical cancer: analysis of prospective multicenter SENTICOL cohort. *Gynecol Oncol.* 2015;137:134–9.
4. Reinhart MB, Huntington CR, Blair LJ, Heniford BT, Augenstein VA. Indocyanine green: historical context, current applications, and future consideration. *Surg Innov.* 2016;23:166–75.
5. Wada H, Hyun H, Vargas C, et al. Sentinel lymph node mapping of liver. *Ann Surg Oncol.* 2015;22:1147–55.
6. Sugie T, Kinoshita T, Masuda N, et al. Evaluation of the clinical utility of the ICG fluorescence method compared with the radioisotope method for sentinel lymph node biopsy in breast cancer. *Ann Surg Oncol.* 2016;23:44–50.
7. Bats AS, Mathevet P, Buenerd A, et al. The sentinel node technique detects unexpected drainage pathways and allows nodal ultrastaging in early cervical cancer: insights from the multicenter prospective SENTICOL study. *Ann Surg Oncol.* 2013;20:413–22.
8. Horn LC, Einenkel J, Hockel M, et al. Recommendations for the handling and oncologic pathology report of lymph node specimens submitted for evaluation of metastatic disease in gynecologic malignancies. *Pathologe.* 2005;26:266–72.
9. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Version 2.2015. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

10. Koh WJ, Greer BE, Abu-Rustum NR, et al. Cervical cancer, version 2.2015. Featured updates to the NCCN guideline. *JNCCN.* 2015;13:395–404.
11. 11. Cormier B, Diaz JP, Shih K, et al. Establishing a sentinel lymph node mapping algorithm for the treatment of early cervical cancer. *Gynecol Oncol.* 2011;122:275–80.
12. Cibula D, Oonk MHM, Abu Rustum NR. Sentinel node biopsy in the management of gynecologic cancer. *Curr Opin Obstet Gynecol.* 2015;27:66–72.
13. Kadkhodayan S, Hasanzadeh M, Treglia G, et al. Sentinel node biopsy for lymph nodal staging of uterine cervix cancer: a systematic review and meta-analysis of the pertinent literature. *Eur J Surg Oncol.* 2015;41:1–20.
14. Lecuru F, Mathevet P, Querleu D, et al. Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. *J Clin Oncol.* 2011;29:1686–91.
15. Cibula D, Abu-Rustum NR, Dusek L, et al. Bilateral ultrastaging of sentinel lymph node in cervical cancer: lowering the false-negative rate and improving the detection of micrometastasis. *Gynecol Oncol.* 2012;127:462–6.
16. Cibula D, Abu-Rustum NR, Dusek L, et al. Prognostic significance of low volume sentinel lymph node disease in early-stage cervical cancer. *Gynecol Oncol.* 2012;124:496–501.
17. Furukawa N, Oi H, Yoshida S, Shigetomi H, Kanayama S, Kobayashi H. The usefulness of photodynamic eye for sentinel lymph node identification in patients with cervical cancer. *Tumori.* 2010;96:936–40.
18. Rossi EC, Ivanova A, Boggess JF. Robotically assisted fluorescence-guided lymph node mapping with ICG for gynecologic malignancies: a feasibility study. *Gynecol Oncol.* 2012;124;1:78–82.
19. Jewell EL, Huang JJ, Abu-Rustum NR, et al. Detection of sentinel lymph nodes in minimally invasive surgery using indocyanine green and near-infrared fluorescence imaging for uterine and cervical malignancies. *Gynecol Oncol.* 2014;133:274–7.
20. Plante M, Touhami O, Trinh XB, et al. Sentinel node mapping with indocyanine green and endoscopic near-infrared fluorescence imaging in endometrial cancer. A pilot study and review of the literature. *Gynecol Oncol.* 2015;137:443–7.
21. Imboden S, Papadia A, Nauwerk M, et al. A comparison of radiocolloid and indocyanine green fluorescent imaging sentinel lymph node mapping in patients with cervical cancer undergoing laparoscopic surgery. *Ann Surg Oncol.* 2015;22:4198–203.
22. Buda A, Crivellaro C, Elisei F, et al. Impact of indocyanine green (ICG) for sentinel node mapping in early stage endometrial and cervical cancer: comparison with conventional radiotracer Tc-99m and/or blue dye. *Ann Surg Oncol.* 2015. doi:10.1245/s10434-015-5022-1.
23. Khoury-Collado F, Glaser GE, Zivanovic O, et al. Improving sentinel node detection rate in endometrial cancer: how many cases are needed? *Gynecol Oncol.* 2009;115:453–5.
24. Gurtzacuzan L, Jimenez W, Nofechmozes S, et al. Sentinel lymph node biospy vs lymphadenectomy in early stage cervical cancer: is it time to change the gold standard? *Gynecol Oncol.* 2010;116:28–32.
25. 25. Schiavone MB, Zivanovic O, Zhou Q, et al. Survival of patients with uterine carcinosarcoma undergoing sentinel lymph node mapping. *Ann Surg Oncol.* 2016;23:196–202.
26. St Clair CM, Erikkson AG, Ducie GA, et al. Low-volume lymph nodes metastasis discovered during sentinel lymph node mapping for endometrial cancer. *Ann Surg.* 2016;23:1653–9.
27. Ercoli A, Dalmas V, Iannone V, et al. The lymphatic drainage of the uterine cervix in adult fresh cadavers: anatomy and surgical implications. *Eur J Surg Oncol.* 2010;36:298–303.
28. Papadia A, Imboden S, Siegenthaler F, et al. Laparoscopic indocyanine green sentinel lymph node mapping in endometrial cancer. *Ann Surg Oncol.* 2016. doi:10.1245/s10434-016-5090-x.
29. Daric MC, Gomez-Hidalgo MR, Westin SN, et al. Role of indocyanine green in sentinel node mapping in gynecologic cancer: is fluorescence imaging the new standard? *J Min Inv Gynecol.* 2016;23:186–93.
30. Ghezzi F, Casarin J, Uccella S. Mini-laparoscopic sentinel node detection in endometrial cancer: further reducing invasiveness for patients with early stage disease. *Ann Surg Oncol.* 2015;22(Suppl 3):342.